We claim:

1. A device for detecting cells or molecules on an electrode surface through measurement of impedance changes resulting from attachment or binding of said cells or molecules to said electrode surface, which device comprises:

   a non-conductive substrate having two opposing ends along a longitudinal axis;

   a plurality of electrode arrays positioned on said substrate, wherein each electrode array comprises at least two electrodes, and further wherein each electrode is separated from at least one adjacent electrode by an area of non-conductive material, said electrode having a width at its widest point of more than about 1.5 and less than about 10 times the width of said area of non-conductive material; and

   electrically conductive traces extending substantially longitudinally to one of said two opposing ends of said substrate, and further wherein each trace is in electrical communication with at least one of said electrode arrays.

2. The device according to Claim 1, wherein the substrate comprises glass, sapphire, silicon dioxide on silicon, or a polymer.

3. The device according to Claim 2, wherein the substrate is configured as a flat surface.

4. The device according to Claim 3, further comprising a plurality of receptacles, wherein each receptacle is disposed on the nonconductive substrate in a perpendicular orientation thereto, further wherein each receptacle forms a fluid-tight container and least one container is associated with an electrode array on the substrate.

5. The device according to Claim 1, further wherein up to half of the electrical traces extend to one end of the substrate, while the remaining electrical traces extend to the other end of the substrate.

6. The device according to Claim 1, further comprising electrical traces between adjacent electrode arrays.

7. The device according to Claim 1, wherein the electrodes of each electrode array are of equal widths.

8. The device according to Claim 1, wherein each of the electrodes has a width of about 90 microns at its widest point.

9. The device according to Claim 8, wherein a gap between adjacent electrodes is about 20 microns.

10. The device according to Claim 1, wherein each electrode array comprises a plurality of evenly spaced electrodes.

11. The device according to Claim 10, wherein each array of electrodes is organized in an interdigitated fashion.

12. The device according to Claim 10, wherein each array of electrodes is organized in a concentric, sinusoidal, or castellated fashion.

13. The device according to Claim 10, further wherein at least one bus is associated with up to half of the plurality of electrodes in each electrode array.

14. The device according to Claim 13, wherein the bus is separated from said array of electrodes by an area of nonconductive material.

15. The device according to Claim 13, wherein the bus comprises an electrode which extends around up to half the perimeter of the electrode array.

16. The device according to Claim 15, further comprising a plurality of receptacles, wherein each receptacle is disposed on the nonconductive substrate in a perpendicular orientation thereto, further wherein each receptacle forms a fluid-tight container and each electrode array on the substrate is associated with a fluid-tight container.

17. The device according to Claim 16, wherein each container is shaped as a tube with opposing open ends, one end of which being in fluid-tight contact with the substrate.

18. The device according to Claim 17, further wherein the diameter of the container at the end in contact with the substrate is smaller than the diameter of the opposing end.

19. The device according to Claim 18, wherein the containers are arranged on the substrate in honeycomb fashion.

20. The device according to Claim 19, wherein the outer wall of each container at its point of contact with the substrate is up to about 2.5 mm from the outer wall of each adjacent container.

21. The device according to Claim 20, wherein the electrodes of each electrode array are of equal widths.

22. The device according to Claim 21, wherein each of the electrodes has a width of about 90 microns at its widest point.

23. The device according to Claim 22, wherein the width of the area of the nonconductive substrate between adjacent electrodes is about 20 microns.

24. The device according to Claim 21, wherein the width of the area of the nonconductive substrate between adjacent electrodes is no less than 10 microns.

25. The device according to Claim 1, further comprising an impedance analyzer electrically connected to all or a plurality of the electrically conductive traces at their termini on at least one end of the substrate.

26. The device according to Claim 25, wherein the impedance is measured at a frequency ranging from about 1 Hz to about 1 MHz.

27. The device according to Claim 1, wherein the electrically conductive traces within the substrate are covered with an insulating layer.

28. The device according to Claim 1, wherein the electrically conductive traces are further disposed in a second plane of the substrate.

29. The device according to Claim 19, wherein the containers together form a multi-well bottomless microtiter plate.

30. The device according to Claim 29, wherein the number of wells present in the bottomless microtiter plate is a number between 6 and 1,536.

31. The device according to Claim 19, wherein less than all of the containers are associated with an active electrode array.

32. The device according to Claim 30, wherein less than all of the containers are associated with an active electrode array.

33. The device according to Claim 1, wherein each of the electrical traces is up to 10 mm from each nearest adjacent electrical trace.

34. The device according to Claim 19, wherein the diameter of one or more containers is, at the container end disposed on the substrate, between about 3 and 7 mm.

35. The device according to Claim 1, wherein the electrodes are fabricated on the substrate by a laser ablation process.

36. The device according to Claim 1, wherein at least one of the electrodes is individually addressed.

37. The device according to Claim 1, further comprising: one or more capture reagents immobilized on the surfaces of the at least two electrodes in each electrode array, wherein the capture reagents are capable of binding target cells and/or molecules.

38. A method for assaying target cells and/or molecules in a sample, which method comprises:

a) contacting one or more electrode arrays of the device of Claim 1 to a sample containing or suspected of containing target cells and/or molecules; and,

b) determining whether a change in impedance occurs between or among electrodes in one or more said electrode arrays;

wherein a detectable change of impedance is indicative of the presence of target cells and/or molecules in said sample, and capture of said cells and/or molecules on the surface of said one or more electrode arrays.

39. The method according to Claim 38, wherein the sample is a biological sample comprising culture media sufficient for target cell growth.

40. The device according to Claim 1, further comprising: an impedance analyzer and connection means for establishing electrical communication between the electrically conductive traces and the impedance analyzer.

41. The device according to Claim 40, wherein the connection means comprises a mechanical clip adapted to securely engage the substrate and to form electrical contact with a trace.

42. The device according to claim 41, wherein the mechanical clip is adapted to form an electrical connection with a printed-circuit board (PCB).

43. The device according to Claim 1, wherein the target cells or molecules are captured on an electrode surface.

44. The device according to Claim 4, wherein a perimeter of the container is contained within the outer perimeter of the electrode arrays.

45. The device according to Claim 7, wherein each of the electrodes has a width between about 50 and about 100 microns at its widest point.

46. The device according to Claim 7, wherein the width of the gap between adjacent electrodes is between about 10 and about 30 microns.

47. The device according to Claim 13, further comprising a plurality of receptacles, wherein each receptacle is disposed on the substrate in a perpendicular orientation thereto, further wherein each receptacle forms a fluid-tight container, and at least one receptacle is contained within a perimeter formed by the buses at a plane of contact between the receptacles and the substrate.

48. The device according to Claim 53, wherein each container is shaped as a tube with opposing open ends, one end of which being in fluid-tight contact with the substrate.

49. The device according to Claim 48, wherein the diameter of the container at the end in contact with the substrate is smaller than the diameter of the opposing end.

50. The device according to Claim 47, wherein the containers are arranged on the substrate in honeycomb fashion.

51. The device according to Claim 50, wherein the outer wall of each container at its point of contact with the substrate is up to about 2.5 mm from the outer wall of each adjacent container.

52. The device according to Claim 51, wherein the electrodes of each electrode array are of equal widths.

53. The device according to Claim 52, wherein each of the electrodes has a width of about 90 microns at its widest point.

54. The device according to Claim 53, wherein the width of the area of nonconductive substrate between adjacent electrodes is about 20 microns.

55. The device according to Claim 54, wherein the width of the area of nonconductive substrate between adjacent electrodes is no less than 10 microns.

56. The device according to Claim 1, wherein the electrodes comprises indium tin oxide (ITO), chromium, gold, copper, nickel, platinum, silver, titanium, steel, and aluminum.

57. The device according to Claim 1, wherein the electrodes are optically transparent.

58. The device according to Claim 1, wherein the non-conductive substrate is a porous substrate.

59. The device according to Claim 1, wherein the device is used for detecting cells and the electrode width is between about 0.5 times and about 10 times the size of cells.

60. The device according to Claim 1, wherein the device is used for detecting cells and the gap between adjacent electrodes is between about 0.2 times and about 3 times the size of cells.

61. The device according to Claim 1, wherein the device is used for detecting cells and the electrode surface is modified with a cell-adhesion promotion moiety.

62. The device according to Claim 61, wherein the cell-adhesion promotion moiety is selected from the group consisting of a self-assembly-monomolecular (SAM) layer, one or more extracellular matrix components, a protein, a polymer layer and a charged group.

63. The device according to Claim 62, wherein the protein promotes specific cell attachment to the electrode surface.

64. The device according to Claim 62, wherein the protein promotes non-specific cell attachment to the electrode surface.

65. The device according to Claim 1, wherein the device is used for detecting cells and the non-electrode surface is modified with a cell-adhesion repelling moiety.

66. The device according to Claim 4, wherein for at least one container associated with an electrode array, the sensor area occupies at least 50%, 70%, 80%, 90%, 95%, or 100% of the surface region that is enclosed within the container.

67. The device according to Claim 25, wherein the electrical connection between the impedance analyzer and the electrically conductive traces is via a switching circuit.

68. The device according to Claim 42, further comprising a POGO-pin structure wherein POGO pins are connected to connection pads comprised on the PCB.

69. A method of producing a device according to Claim 1, comprising:

a) providing a non-conductive substrate;

b) depositing an electrically conductive film on said substrate; and

c) patterning the electrically conductive film to make the plurality of electrode arrays using laser ablation of the conductive film.

70. The method of claim 69, further comprising cleaning the substrate after laser ablation of the electrically conductive film.

71. The method of claim 69, wherein the substrate comprising the patterned plurality of electrode arrays is assembled to a bottomless multi-well plate to form an electrode-containing multi-well plate.

72. A device for monitoring cell-substrate impedance, which device comprises:

a) a non-conducting substrate;

b) at least two electrode structures fabricated to the same side of said substrate, wherein:

i) each of said at least two electrode structures has at least two electrode elements; and

ii) said at least two electrode structures have substantially same surface area; and

iii) said electrode elements and gaps between said electrode elements are arranged so that there is a high probability for cells to contact an electrode element when said cells are introduced onto said device; and

c) at least two connection pads located on said substrate,

wherein said device has a surface suitable for cell attachment or growth and said cell attachment or growth on said device results in detectable change in impedance between or among said electrode elements.

73. The device according to Claim 72, wherein the substrate comprises glass, sapphire, silicon dioxide on silicon, plastics, or a polymer.

74. The device according to Claim 72, wherein the non-conducting substrate is a porous substrate.

75. The device according to Claim 72, wherein the electrode element has a geometry selected from the group consisting of circle-on-line, diamond-on-line, interdigitated, castellated and sinusoidal geometry.

76. The device according to Claim 72, wherein the electrode elements and gaps between the electrode elements are arranged so that more than 50% of the cells that are introduced onto the device contact an electrode element.

77. The device according to Claim 72, wherein the electrodes comprises indium tin oxide (ITO), chromium, gold, copper, nickel, platinum, silver, titanium, steel, and aluminum.

78. The device according to Claim 72, wherein the electrodes are optically transparent.

79. The device according to Claim 72, wherein the electrode width is between about 0.5 times and about 10 times the size of cells.

80. The device according to Claim 72, wherein the gap between adjacent electrode elements is between about 0.2 times and about 3 times the size of cells.

81. The device according to Claim 72, wherein the electrode surface is modified with a cell-adhesion promotion moiety.

82. The device according to Claim 81, wherein the cell-adhesion promotion moiety is selected from the group consisting of a self-assembly-monomolecular (SAM) layer, one or more extracellular matrix components, a protein, a polymer layer and a charged group.

83. The device according to Claim 82, wherein the protein promotes specific cell attachment to the electrode surface.

84. The device according to Claim 82, wherein the protein promotes non-specific cell attachment to the electrode surface.

85. The device according to Claim 72, wherein the device is used for detecting cells and the non-electrode surface is modified with a cell-adhesion repelling moiety.

86. The device according to Claim 72, further comprising a plurality of receptacles, wherein each receptacle is disposed on the nonconducting substrate in a perpendicular orientation thereto, further wherein each receptacle forms a fluid-tight container and at least one container is associated with two electrode structures.

87. A method of making the device of Claim 72, comprising:
   a) providing a non-conducting substrate;
   b) depositing an electrically conductive film on said substrate; and
   c) patterning the electrically conductive film to make electrode structures using laser ablation of the conductive film.

88. The method of claim 72, further comprising cleaning the substrate after laser ablation of the conductive film.

89. The method of claim 72, wherein the substrate comprising patterned electrode structures is assembled to a bottomless multi-well plate to form an electrode-containing multi-well plate.

90. A device for monitoring cell-substrate impedance, which device comprises:

a) a nonconducting substrate;

b) a plurality of electrode structure units fabricated to the same side of said substrate, each of said unit comprises at least two electrode structures and wherein each of said electrode structures has at least two electrode elements;

c) a bus that connects said electrode elements within said electrode structure, wherein said bus is not exposed to a sample liquid added to said device; and

d) a plurality of receptacles wherein each receptacle is disposed on said non-conducting substrate in a perpendicular orientation thereto, further wherein each receptacle forms a fluid-tight container and at least one of said containers is associated with at least one electrode structure unit on said substrate,

wherein said device has a surface suitable for cell attachment or growth and said cell attachment or growth on said device results in detectable change in impedance between or among said electrode structure units.

91. The device according to Claim 96, wherein the substrate comprises glass, sapphire, silicon dioxide on silicon, plastics, or a polymer.

92. The device according to Claim 96, wherein the non-conducting substrate is a porous substrate.

93. The device according to Claim 90, wherein the electrode element has a geometry selected from the group consisting of circle-on-line, diamond-on-line, interdigitated, castellated and sinusoidal geometry.

94. The device according to Claim 90, wherein the electrode elements and gaps between the electrode elements are arranged so that more than 50% of the cells that are introduced onto the device contact an electrode element.

95. The device according to Claim 90, wherein the electrodes comprises indium tin oxide (ITO), chromium, gold, copper, nickel, platinum, silver, titanium, steel, and aluminum.

96. The device according to Claim 90, wherein the electrodes are optically transparent.

97. The device according to Claim 90, wherein the bus is covered with an insulating material.

98. The device according to Claim 90, wherein the fluid-tight containers are in a multi-well microplate format.

99. The device according to Claim 98, wherein the electrode bus lies outside the bottom surface of the well.

100. The device according to Claim 98, wherein the multi-well microplate is selected from the group consisting of a 6-, 12-, 24-, 48-, 96-, 192-, 384-, 768- and 1,536-well plate.

101. The device according to Claim 90, wherein the surface of the electrode structure units is modified with a cell-adhesion promotion moiety.

102. The device according to Claim 101, wherein the cell-adhesion promotion moiety is selected from the group consisting of a self-assembly-monomolecular (SAM) layer, a protein, a polymer layer and a charged group.

103. The device according to Claim 102, wherein the SAM layer is an alkanethiolate on gold or an alkylsiloxane on SiO_2 or SiOx.

104. The device according to Claim 102, wherein the protein promotes specific cell attachment to the surface of the electrode structure units.

105. The device according to Claim 102, wherein the protein promotes non-specific cell attachment to the surface of the electrode structure unit.

106. The device according to Claim 90, wherein the surface area of non-electrode-element is modified with a cell-adhesion repelling moiety.

107. The device according to Claim 90, wherein each receptacle forms a fluid-tight container associated with at least one electrode structure unit on said substrate.

108. The device according to Claim 90, wherein at least one of said containers is not associated with an electrode structure unit on the substrate.

109. The device according to Claim 90, which further comprises an impedance analyzer electrically connected to the substrate.

110. The device according to Claim 109, wherein the impedance analyzer is electrically connected to the substrate via a printed-circuit board (PCB).

111. The device according to Claim 110, wherein PCB is electrically connected to the substrate via a metal clip.

112. The device according to Claim 111, wherein the fluid-tight containers are in a multi-well microplate format.

113. The device according to Claim 112, wherein the multi-well microplate is selected from the group consisting of a 6-, 12-, 24-, 48-, 96-, 192-, 384-, 768- and 1,536- well plate.

114. The device according to Claim 110, further comprising a POGO-pin structure wherein POGO pins are connected to connection pads comprised on the PCB.

115. A method of making a device of claim 90, comprising:

a) providing a non-conducting substrate;

b) depositing an electrically conductive film on said substrate; and

c) patterning the electrically conductive film to make the plurality of electrode structure units using laser ablation of the conductive film.

116. The method of claim 115, further comprising cleaning the substrate after laser ablation of the conductive film.

117. The method of claim 115, wherein the substrate comprising patterned plurality of electrode structure units is assembled to a bottomless multi-well plate to form an electrode-containing multi-well plate.

118. A device for monitoring cell-substrate impedance, which device comprises:

a) a plurality of wells;

b) at least one of the plurality of wells comprises at least two electrode structures on the bottom surface of the well; wherein

i) each of said at least two electrode structures has at least two electrode elements fabricated on a nonconducting substrate forming the bottom of the wells;

ii) said at least two electrode structures have substantially same surface area; and

c) connection means for connecting the electrode structures to an impedance measurement circuit via an electronic switch,

wherein said device has a surface suitable for cell attachment or growth and said cell attachment or growth on said devices results in detectable change in impedance between or among said electrode structures.

119. The device according to Claim 118, wherein said nonconducting substrate further comprises connection pads along an edge of the substrate.

120. The device according to Claim 119, wherein connection means comprises a printed circuit board (PCB), said PCB comprises electrical connection pads that are electrically connected to connection pads along an edge of the substrate.

121. The device according to Claim 120, wherein said PCB has connection circuitry on one side.

122. The device according to Claim 120, wherein said PCB has connection circuitry on both sides.

123. The device according to Claim 120, wherein the electrical connection between the PCB and connection pads along an edge of the substrate is via a metal clip.

124. The device according to Claim 120, wherein connection means comprises a flex circuit, said flex circuit comprises electrical connection pads that are electrically connected to connection pads along an edge of the substrate.

125. The device according to Claim 119, wherein connection means comprises a metal clip, said metal clip are electrically connected to connection pads along an edge of the substrate.

126. The device according to Claim 120, wherein connection means further comprises a POGO-pin structure wherein POGO-pins are electrically connected to connection pads on the PCB.

127. The device according to Claim 124, wherein connection means further comprises a POGO-pin structure wherein POGO-pins are electrically connected to connection pads on the flex circuit.

128. The device according to Claim 125, wherein connection means further comprises a POGO-pin structure wherein POGO-pins are connected to metal clip.

129. A method for monitoring cell attachment or growth, which method comprises:

a) providing a device of Claim 86;

b) attaching cells to or growing cells on the surface of said device; and

c) monitoring a change of impedance between or among the electrode structures to monitor said cell attachment or growth on said device.

130. The method according to Claim 129, which further comprises determining the amount or number of cells that are attached to or grown on the device from the monitored impedance.

131. The method according to Claim 129, which further comprises deriving a cell number index from the monitored impedance.

132. The method according to Claim 131, wherein the cell number index is derived from a process selected from the group consisting of process 1 comprising:

a) at each measured frequency, calculating the resistance ratio by dividing the measured resistance when cells are attached to the electrodes by the baseline resistance;

b) determining the maximum value in the resistance ratio over the frequency spectrum; and

c) subtracting one from the maximum value in the resistance ratio, wherein a zero or near-zero "cell number index" indicates that no cells or very small number of cells are present on or attached to the electrode surfaces and a higher value of "cell number index" indicates that, for same type of the cells and cells under similar physiological conditions, more cells are attached to the electrode surfaces;

process 2 comprising:

a) at each measured frequency, calculating the resistance ratio by dividing the measured resistance when cells are attached to the electrodes by the baseline resistance;

b) determining the maximum value in the resistance ratio over the frequency spectrum; and

c)taking a log-value of the maximum value in the resistance ratio,

wherein, a zero or near-zero "cell number index" indicates that no cells or very small number of cells are present on or attached to the electrode surfaces and a higher value of "cell number index" indicates that, for same type of the cells and cells under similar physiological conditions, more cells are attached to the electrode surfaces;

process 3 comprising:

a) at each measured frequency, calculating the reactance ratio by dividing the measured reactance when cells are attached to the electrodes by the baseline reactance;

b)determining the maximum value in the reactance ratio over the frequency spectrum; and

c) subtracting one from the maximum value in the resistance ratio,

wherein a zero or near-zero "cell number index" indicates that no cells or very small number of cells are present on or attached to the electrode surfaces and a higher value of "cell number index" indicates that, for same type of the cells and cells under similar physiological conditions, more cells are attached to the electrode surfaces,

and process 4 comprising:

a)at each measured frequency, calculating the resistance ratio by dividing the measured resistance when cells are attached to the electrodes by the baseline resistance;

b) calculating the relative change in resistance in each measured frequency by subtracting one from the resistance ratio; and

c) integrating all the relative-change value,

wherein the "cell-number index" is derived based on multiple-frequency points, a zero or near-zero "cell number index" indicates that no cells or very small number of cells are present on the electrodes and a higher value of "cell number index" indicates that, for same type of the cells and cells under similar physiological conditions, more cells are attached to the electrodes.

133. The method according to Claim 129, wherein the cell attachment or growth is monitored on a real time basis.

134. The method according to Claim 129, wherein the cell attachment or growth is monitored in the presence and absence of a test compound and the method is used to determine whether said test compound modulates attachment or growth of the cells.

135. The method according to Claim 129, wherein the cell attachment or growth is stimulated by a growth factor and the method is used to screen the test compound for a growth factor antagonist.

136. A method for monitoring effect of a test compound on cell attachment or growth, which method comprises:

a) providing a device of Claim 86;

b) attaching cells to or growing cells in a plurality of containers of said device wherein each of said plurality of containers is associated with at least two electrode structures and contains substantially same number of same type of cells and a different concentration of a test compound; and

c) monitoring a change of impedance between or among the electrode structures as a function of time to monitor the effect of said test compound on cell attachment or growth.

137. The method according to Claim 136, which further comprises determining number of viable cells in each container.

138. The method according to Claim 136, which further comprises determining whether the test compound is an antagonist to the growth of the cells.

139. The method according to Claim 136, which further comprises determining the dose response of the test compound.

140. A method for monitoring cell attachment or growth, which method comprises:

a) providing a device of Claim 90;

b) attaching cells to or growing cells on the surface of said device;

and

c) monitoring a change of impedance between or among the electrode structures within each of the plurality of electrode structure units to monitor said cell attachment or growth on said device.

141. The method according to Claim 140, which further comprises determining the amount or number of cells that are attached to or grown on the device from the monitored impedance.

142. The method according to Claim 140, which further comprises deriving a cell number index from the monitored impedance.

143. The method according to Claim 142, wherein the cell number index is derived from a process selected from the group consisting of process 1 comprising:

i) at each measured frequency, calculating the resistance ratio by dividing the measured resistance when cells are attached to the electrodes by the baseline resistance;

ii) determining the maximum value in the resistance ratio over the frequency spectrum; and

iii) subtracting one from the maximum value in the resistance ratio,

wherein a zero or near-zero "cell number index" indicates that no cells or very small number of cells are present on or attached to the electrode surfaces and a higher value of "cell number index" indicates that, for same type of the cells and cells under similar physiological conditions, more cells are attached to the electrode surfaces;

process 2 comprising:

i) at each measured frequency, calculating the resistance ratio by dividing the measured resistance when cells are attached to the electrodes by the baseline resistance;

ii) determining the maximum value in the resistance ratio over the frequency spectrum; and

iii) taking a log-value of the maximum value in the resistance ratio,

wherein, a zero or near-zero "cell number index" indicates that no cells or very small number of cells are present on or attached to the electrode surfaces and a higher value of "cell number index" indicates that, for same type of the cells and cells under similar physiological conditions, more cells are attached to the electrode surfaces;

process 3 comprising:

i) at each measured frequency, calculating the reactance ratio by dividing the measured reactance when cells are attached to the electrodes by the baseline reactance;

ii) determining the maximum value in the reactance ratio over the frequency spectrum; and

iii) subtracting one from the maximum value in the resistance ratio,

wherein a zero or near-zero "cell number index" indicates that no cells or very small number of cells are present on or attached to the electrode surfaces and a higher value of "cell number index" indicates that, for same type of the cells and cells under similar physiological conditions, more cells are attached to the electrode surfaces,

and process 4 comprising:

i) at each measured frequency, calculating the resistance ratio by dividing the measured resistance when cells are attached to the electrodes by the baseline resistance;

ii) calculating the relative change in resistance in each measured frequency by subtracting one from the resistance ratio; and

iii) integrating all the relative-change value,

wherein the "cell-number index" is derived based on multiple-frequency points, a zero or near-zero "cell number index" indicates that no cells or very small number of cells are present on the electrodes and a higher value of "cell number index" indicates that, for same type of the cells and cells under similar physiological conditions, more cells are attached to the electrodes.

144. The method according to Claim 140, wherein the cell attachment or growth is monitored on a real time basis.

145. The method according to Claim 140, wherein the cell attachment or growth is monitored in the presence and absence of a test compound and the method is used to determine whether said test compound modulates attachment or growth of the cells.

146. The method according to Claim 140, wherein the cell attachment or growth is stimulated by a growth factor and the method is used to screen the test compound for a growth factor antagonist.

147. A method for monitoring effect of a test compound on cell attachment or growth, which method comprises:

a) providing a device of Claim 90;

b) attaching or growing cells in a plurality of containers of said device wherein each of said plurality of contains is associated with an electrode structure unit and contains substantially same number of same type of cells and serially different concentration of a test compound; and

c) monitoring a change of impedance between or among the electrode structures of an electrode structure unit as a function of time to monitor the effect of said test compound on cell attachment or growth.

148. The method according to Claim 147, which further comprises determining number of viable cells in each container.

149. The method according to Claim 147, which further comprises determining whether the test compound is an antagonist to the growth of the cells.

150. The method according to Claim 147, which further comprises determining the dose response of the test compound.

151. A method for making a multi-well plate, which method comprises:

a) providing a non-conducting substrate;

b) depositing an electrically conductive film on said substrate;

c) patterning the electrically conductive film to make electrodes or electrode structures using laser ablation of the conductive film; and

d) assembling the thin-film patterned substrate to a bottomless multi-well plate to form an electrode-containing multi-well plate.

152. The method according to Claim 151, where the substrate is made of a material selected from glass, silicon dioxide on silicon, polymer, plastic, ceramic, fiber glass and a combination thereof.

153. The method according to Claim 151, where the substrate is cleaned to remove dusts and other particles before depositing the electrically conductive film.

154. The method according to Claim 151, wherein the electrically conductive film is a metal film.

155. The method according to Claim 151, wherein the electrically conductive film is optically transparent.

156. The method according to Claim 151, wherein the electrically conductive film has a thickness between 0.03 micron and 1 micron.

157. The method according to Claim 151, wherein a laser ablation mask is used in the laser ablation in patterning the electrodes or electrode structures.

158. The method according to Claim 151, wherein the laser ablation is conducted with an excimer laser.

159. The method according to Claim 151, wherein a sacrificial layer is used during the laser ablation.

160. The method according to Claim 151, wherein the thin-film patterned substrate is cleaned to remove re-deposition from the laser ablation step.

161. The method according to Claim 151, wherein the thin-film patterned substrate is assembled to the bottomless multi-well plate using double-sided pressure sensitive adhesives or a liquid adhesive.

162. A method for electroporating adherent cells, which method comprises:

a) providing a device of Claim 86 comprising a plurality of containers, at least one of said containers comprising at least two electrode structures;

b) attaching or growing cells in said electrode-structures-containing container; and

c) applying electrical voltages pulses to said electrode-structures to result in electroporation of the membrane of said cells adhered to the bottom surface of said electrode-structures containing container.

163. A method for electroporating suspension cells, which method comprises:

a) providing a device of Claim 86 comprising a plurality of containers, at least one of said containers comprising at least two electrode structures;

b) adding cells in suspension to said electrode-structures-containing container; and

c) applying electrical voltages pulses to said electrode-structures to result in electroporation of the membrane of said cells in said electrode-structures-containing container.

164. A method for electroporating adherent cells, which method comprises:

a) providing a device of Claim 90 comprising a plurality of containers, at least one of said containers comprising at least one electrode structure unit;

b) attaching or growing cells in said electrode-structure-unit-containing container; and

c) applying electrical voltages pulses to said electrode-structure-unit to result in electroporation of the membrane of said cells adhered to the bottom surface of aid electrode-structure-unit containing container.

165. A method for electroporating suspension cells, which method comprises:

a) providing a device of Claim 90 comprising a plurality of containers, at least one of said containers comprising at least one electrode structure unit;

b) adding cells in suspension to said electrode-structure-unit-containing container; and

c) applying electrical voltages pulses to said electrode-structure-unit to result in electroporation of the membrane of said cells in said electrode-structure-unit-containing container.

166. A device for assaying target molecules, which device comprises.

a) a nonconducting substrate;

b) at least two electrodes fabricated on said substrate, wherein the surfaces of said electrodes are modified with capture molecules which bind to target molecules in a liquid sample, and

c) at least two connection pads on said substrate, wherein said at least two electrodes are connected respectively to said at least two connection pads,

wherein binding of said target molecules to said capture molecules results in a detectable change in impedance between or among said at least two electrodes.

167. The device according to Claim 166, wherein the at least two electrodes are part of a plurality of electrode arrays positioned on the substrate, wherein each electrode array includes at least two electrodes, and further wherein each electrode is separated from at least one adjacent electrode by an area of non-conductive material, the electrode having a width at its widest point of more than about 1.5 and less than about 10 times the width of the area of non-conductive material.

168. The device according to Claim 166, wherein the at least two electrodes are part of at least two electrode structures fabricated to the same side of the substrate, wherein:

i) each of said at least two electrode structures has at least two electrode elements; and

ii) said at least two electrode structures have substantially same surface area.

169. The device according to Claim 166, wherein the at least two electrodes are part of a plurality of electrode structure units fabricated to the same side of the substrate, each of the unit comprising at least two electrode structures and wherein each of the electrode structures has at least two electrode elements.

170. The device according to Claim 166, wherein nonconducting substrate comprises glass, sapphire, silicon-dioxide-on-silicon, a plastic, or a polymer.

171. The device according to Claim 166, wherein nonconducting substrate comprises polyimide, polyester, or polycarbonate.

172. The device according to Claim 166, wherein at least two electrodes comprise gold, silver, platinum, chromium, aluminum, copper, indium tin oxide, steel, or titanium.

173. The device according to Claim 166, wherein at least two electrodes are in an interdigitated configuration.

174. The device according to Claim 166, wherein at least two electrodes have circle-on-line, diamond-on-line, castellated, or sinusoidal geometries.

175. The device according to Claim 166, wherein width of said electrodes is from about 20 microns to about 500 microns.

176. The device according to Claim 166, wherein the at least two electrodes are fabricated on the substrate by laser ablation.

177. The device according to Claim 166, which is in a form of an electrode strip with the ratio of the major axis of the strip to the minor axis of the strip being at least 5.

178. The device according to Claim 177, wherein the electrode strip is partially or completely covered by a housing.

179. The device according to Claim 166, which further comprises an impedance analyzer connected to the connection pads.

180. The device according to Claim 166, which further comprises a bottomless multi-well microplate that is bound to the nonconducting substrate, wherein at least one well contains said at least two electrodes on the bottom of the well.

181. The device according to Claim 180, wherein the multi-well microplate is selected from the group consisting of a 6-, 12-, 24-, 48-, 96-, 192-, 384-, 768- and 1,536-well plate.

182. The device according to Claim 166, which has multiple pairs of electrodes spatially arranged according to wells of a multi-well microplate.

183. The device according to Claim 182, wherein the multi-well microplate is selected from the group consisting of a 6-, 12-, 24-, 48-, 96-, 192-, 384-, 768- and 1,536-well plate.

184. The device according to Claim 166, which further comprises the target molecules that are bound to the capture molecules.

185. The device according to Claim 166, wherein the impedance is measured at a frequency ranging from about 1 Hz to about 1 MHz.

186. The device according to Claim 166, wherein the ratio of surface areas between the largest electrode and the smallest electrode is less than 10.

187. The device according to Claim 166, wherein the surface of said at least two electrodes is modified with capture molecules via chemical or physical methods.

188. The device according to Claim 187, wherein said physical methods comprise one or more of the followings: passive absorption, spin coating of molecule solution followed by drying, spotting of molecule solutions on the electrodes.

189. The device according to Claim 187, wherein said chemical methods comprise one or more of the followings: molecular self assembly, chemical reactions on the electrode surface.

190. The device according to Claim 166, wherein the surface of said at least two electrodes is modified with capture molecules via linkage molecules.

191. The device according to Claim 190, wherein the linkage molecules comprise: biotin-straptoavidin pairs, antibody-antigen pairs, antibody-protein pairs, sugar-lecithin pairs, or receptor-ligand pairs.

192. The device according to Claim 166, wherein the electrode sensor area occupies at least 50% of the surface area of the device that is contacted by sample liquid during a molecular assay.

193. The device according to Claim 166, wherein the electrode sensor area occupies at least 90% of the surface area of the device that is contacted by sample liquid during a molecular assay.

194. The device according to Claim 166, wherein the electrode sensor area occupies at least 99% of the surface area of the device that is contacted by sample liquid during a molecular assay.

195. The device according to Claim 166, wherein the target molecules are labeled.

196. The device according to Claim 195, wherein the label of the labeled target molecules comprises an impedance change signal amplifying molecule.

197. The device according to Claim 196, wherein the impedance change signal amplifying molecule catalyzes a molecular reaction, resulting in a product that is measured by electronic impedance detection.

198. The device according to Claim 196, wherein the impedance change signal amplifying molecule is an enzyme.

199. The device according to Claim 198, wherein the enzyme catalyzes a reaction forming a product that precipitates on the surface of electrodes comprised in the device.

200. A multi-well microplate for assaying target molecules, which microplate comprises a plurality of wells, at least one of the wells comprises a device of Claim 166.

201. A multi-well microplate according to Claim 200, at least two of the wells comprise a device of Claim 166.

202. A multi-well microplate according to Claim 201, all the wells comprise a device of Claim 166.

203. A multi-well microplate according to Claim 200, at least one of the wells does not comprise electrodes.

204. A method for assaying target molecules in a sample liquid, which method comprises:

a) providing a device of Claim 166;

b) providing a sample liquid comprising or suspected of comprising target molecules;

c) contacting said sample liquid comprising or suspected of comprising said target molecules to said device to allow binding of said target molecules, if present in said sample liquid, to said capture molecules; and

d) monitoring a change of impedance between or among the electrodes to assess the presence and/or amount of said target molecules in said sample liquid.

205. The method according to Claim 204, wherein the target molecules, if present in the sample liquid, are labeled and allowed to bind to the capture molecules.

206. The method according to Claim 204, which is used to asses the amount or concentration of the target molecules.

207. The method according to Claim 206, wherein the target molecules are assayed on a real time basis.

208. The method according to Claim 204, wherein the capture molecules are selected from the group consisting of nucleic acids, proteins and antibodies.

209. The method according to Claim 204, wherein the target molecules are selected from the group consisting of proteins, antigens, antibodies, nucleic acids and chemical molecules.

210. The method according to Claim 203, wherein the labels of the labeled target molecules are impedance change signal amplifying molecules.

211. The method according to Claim 203, wherein the labels of the labeled target molecules are labeling particles.

212. The method according to Claim 211, wherein the labeling particles are selected from the group consisting of nano-sized particles, micro-sized particles, conductive particles, insulating particles, semi-conducting particles and nano-sized or micro-sized liposomes.

213. The method according to Claim 210, wherein the impedance change signal amplifying molecules are attached to the target molecules directly.

214. The method according to Claim 210, wherein the impedance change signal amplifying molecules are attached to the target molecules indirectly via a linking pair.

215. The method according to Claim 210, wherein the linking pair is selected from the group of biotin-avidin, sugar-lecithin, antibody-antigen and receptor-ligand pair.

216. The method according to Claim 210, wherein the impedance change signal amplifying molecules catalyze a molecular reaction resulting in a product that is measured by electronic impedance detection.

217. The method according to Claim 210, wherein the impedance change signal amplifying molecule is an enzyme.

218. The method according to Claim 217, wherein the enzyme catalyzes a reaction forming a product that precipitates on the surface of electrodes comprised in the device.

219. A method for assaying target molecules in a sample liquid, which method comprises:

a) providing a device of Claim 166;

b) providing a sample liquid comprising or suspected of comprising target molecules;

c) contacting said sample liquid comprising or suspected of comprising said target molecules to said device to allow binding of said target molecules, if present in said sample liquid, to said capture molecules;

d) adding labeling molecules in a solution to said device;

e) incubating the solution in step d) in said device to allow the labeling molecules to bind to the target molecules;

f) monitoring a change of impedance between or among the electrodes to assess the presence and/or amount of said target molecules in said sample liquid.

220. The method according to Claim 219, which further comprises determining the amount or concentration of target molecules.

221. The method according to Claim 219, wherein the labeling molecule is an enzyme.

222. The method according to Claim 221, which further comprises washing off the unbound labeling molecules after step e).

223. The method according to Claim 222, which further comprises adding substrate molecules that is converted to a precipitated product on the surface of the electrodes by the enzyme.

224. An apparatus for monitoring cell migration or growth, which apparatus comprises a nonconducting substrate comprising, on the surface of said substrate, a first area for cell attachment, surrounded by a second electrode area comprising at least two electrodes, wherein said first cell attachment area is separated from said second electrode area by a cell migration barrier, wherein removal of said barrier allows cell migration or growth from said first cell attachment area into said second electrode area, and said cell migration or growth results in a change of impedance between or among electrodes in said second electrode area.

225. The apparatus according to Claim 224, wherein the first cell attachment area is modified with a cell-adhesion promotion moiety.

226. The apparatus according to Claim 224, wherein the first cell attachment area and the second electrode area are concentric.

227. The apparatus according to Claim 224, wherein the cell migration barrier is a well.

228. A method for monitoring cell migration or growth, which method comprises:

a) providing an apparatus of Claim 224;

b) placing cells to be monitored on the first cell attachment area;

c) removing the cell migration barrier and allowing migration or growth of said cells from the first cell attachment area into the second electrode area; and

d) monitoring a change of impedance between or among electrodes in said second electrode area to monitor migration or growth of said cells.

229. The method according to Claim 228, which further comprises determining the amount or number of cells that migrate or grow into the second electrode area.

230. The method according to Claim 228, wherein the cell migration or growth is monitored in the presence and absence of a test compound and the method is used to determine whether said test compound modulates migration or growth of the cells.

231. The method according to Claim 228, wherein the cell migration or growth is stimulated by a migration or growth stimulator and the method is used to screen the test compound for an antagonist of said stimulator.

232. An apparatus for monitoring neurite growth, which apparatus comprises a nonconducting substrate comprising, on its surface, a center neuron anchoring area surrounded by a neurite outgrowth detection area, wherein neurite growth detection area comprises at least two electrodes that are capable of generating a change of impedance between or among said electrodes when at least one of said electrodes is covered by said growing neuron.

233. The apparatus according to Claim 232, wherein the neuron anchoring area is modified with a cell-adhesion promotion moiety.

234. The apparatus according to Claim 232, wherein the neuron anchoring area and the neurite growth detection area are concentric.

235. The apparatus according to Claim 232, wherein the measurement unit comprises a center circular electrode surrounded by multiple circular, segment electrodes.

236. The apparatus according to Claim 232, wherein the measurement unit comprises a center square electrode surrounded by multiple linear segment electrodes.

237. The apparatus according to Claim 232, which further comprise an impedance analyzer capable of monitoring a change of electrode impedance between or among any two or more electrodes.

238. A method for monitoring neurite growth, which method comprises:

a) providing an apparatus of Claim 232;

b) positioning a neuron to be monitored on the neuron anchoring area;

c) allowing growth of said neuron from the neuron anchoring area into the neurite outgrowth detection area; and

d) monitoring a change of impedance between or among electrodes in the neurite outgrowth detection area to monitor growth of said neuron.

239. The method according to Claim 238, which is used to monitor length and numbers of neurites in cultivated neurons.

240. The method according to Claim 238, which is used to monitor the growth of a plurality of neurons simultaneously.

241. The method according to Claim 238, wherein the neurite growth is monitored in the presence and absence of a test compound and the method is used to determine whether said test compound modulates the neurite growth.

242. The method according to Claim 238, wherein the neurite growth is stimulated by a neurite growth stimulator and the method is used to screen the test compound for an antagonist of said stimulator.

243. An apparatus for analyzing a particle, which apparatus comprises a substrate comprising a microchannel and a pair of electrodes located on opposite sides along said microchannel, each of said electrodes having a surface area that equals to or is less than twice the largest cross-sectional area of a particle to be analyzed, wherein passage of said particle through said electrode pair in said microchannel generates a change of impedance between said electrodes that can be used to analyze said particle.

244. The apparatus according to Claim 243, wherein each of the electrodes has a surface area that equals to or is less than the same, a half, or ten percent the largest cross-sectional area of a particle to be analyzed.

245. The apparatus according to Claim 243, wherein each of the electrodes has, along the length of the microchannel, a length that is substantially less than the largest single-dimension of a particle to be analyzed.

246. The apparatus according to Claim 243, wherein the electrodes span the entire height of the microchannel.

247. The apparatus according to Claim 243, which comprises two pairs of the electrodes, said two pairs are separated from each other along the length of the microchannel by a distance that equals to or is less than the largest single-dimension of a particle to be analyzed.

248. The apparatus according to Claim 247, wherein the a change of impedance between the two pairs of the electrodes is measured.

249. The apparatus according to Claim 243, which comprises three pairs of the electrodes, said three pairs separated from each other along the length of the microchannel, wherein the pairs of the electrodes on both ends are used to supply voltages and the pair of the electrodes in the middle is used to generate a change of electrode impedance.

250. The apparatus according to Claim 249, wherein the change of voltage between the middle pair and an end pair is monitored.

251. The apparatus according to Claim 243, which comprises four pairs of the electrodes, said four pairs separated from each other along the length of the microchannel, wherein the two pairs of the electrodes on both ends are used to supply voltages and the two pairs of the electrodes in the middle are used to generate a change of electrode impedance.

252. The apparatus according to Claim 251, wherein the change of voltage between one of the middle pairs and one of the end pairs is monitored.

253. The apparatus according to Claim 243, which further comprise an impedance analyzer.

254. A method for analyzing a particle, which method comprises:

a) providing an apparatus of Claim 243;

b) allowing a particle to be analyzed to pass through the electrode pair in the microchannel to generate a change of impedance between electrodes in said apparatus; and

c) monitoring said change of impedance to analyze said particle.

255. The method according to Claim 254, wherein the particle to be analyzed is a cell.

256. The method according to Claim 255, wherein the cell is selected from the group consisting of an animal cell, a plant cell, a fungal cell, a bacterial cell, a recombinant cell and a cultured cell.

257. The method according to Claim 255, which is used to analyze the nucleic acid content of the cell.

258. The method according to Claim 257, wherein the nucleic acid is DNA.

259. An apparatus for analyzing a particle, which apparatus comprises:

a) a container suitable for containing a solution comprising a particle to be analyzed; and

b) a membrane separating said container into two electrically isolated chambers, said membrane comprising an aperture having a pore size that equals to or is slightly larger than size of said particle and two electrodes suitable for detecting a change of impedance in said solution caused by a transit passage of said particle through said aperture.

260. The apparatus according to Claim 259, wherein the membrane has a thickness from about 1 micron to about 50 microns.

261. The apparatus according to Claim 259, wherein the membrane has a thickness that equals to or is smaller than a diameter of a particle to be analyzed.

262. The apparatus according to Claim 259, wherein the aperture has a pore size of about 2, 5, 10, 15 or 25 microns.

263. The apparatus according to Claim 259, wherein the two electrodes are located on the opposite sides of the membrane.

264. The apparatus according to Claim 259, wherein the two electrodes have a concentric dimension surrounding the aperture.

265. The apparatus according to Claim 259, which comprises a plurality of membranes arranged in series to allow a particle to pass apertures of said membranes sequentially.

266. The apparatus according to Claim 259, which further comprise a means for positioning or aligning a particle or particles.

267. A method for analyzing a particle, which method comprises:

a) providing an apparatus of Claim 259;

b) placing a solution comprising a particle to be analyzed in the container and allowing said particle to pass through the aperture; and

c) detecting a change of impedance in said solution caused by the transit passage of said particle through said aperture to analyze said particle.

268. The method according to Claim 267, which is used to analyze size or dielectric property of the particle.

269. The method according to Claim 267, wherein the particle is labeled with a nano-sized dielectric or electric moiety.

270. The method according to Claim 269, wherein the nano-sized dielectric or electric moiety comprises an antibody that specifically binds to the particle to be analyzed.

271. The method according to Claim 269, wherein the nano-sized dielectric or electric moiety is a gold particle.

272. The method according to Claim 267, wherein the particle to be analyzed is a cell.

273. The method according to Claim 272, wherein the cell is selected from the group consisting of an animal cell, a plant cell, a fungal cell, a bacterial cell, a recombinant cell and a cultured cell.

274. The method according to Claim 272, which is used to analyze size, dielectric property, or viability of the cell.

275. The method according to Claim 272, wherein the cell is labeled with a nano-sized dielectric or electric moiety.

276. The method according to Claim 275, wherein the nano-sized dielectric or electric moiety comprises an antibody that specifically binds to the cell to be analyzed.

277. A system for monitoring cell-substrate impedance and solution conductivity, which system comprises:

a) a substrate defining a plurality of discrete microwells on a substrate surface, at least one of said wells comprising a device of Claim 1 for monitoring cell substrate impedance; and

b) a means for measuring the conductance of a solution medium in each microwell, said means comprising

(i) a pair of electrodes adapted for insertion into a well on said substrate;

(ii) electrical means for applying a low-voltage, alternate current (AC) signal across said electrodes when said electrodes are submerged in said solution medium; and

(iii) electrical means for synchronously measuring the current across said electrodes,

wherein said system can be used to monitor attachment, growth or metabolic activity of cells contained in each well.

278. A system for monitoring cell-substrate impedance and solution conductivity, which system comprises:

a) a substrate defining a plurality of discrete microwells on a substrate surface, at least of said wells comprising a device of Claim 1 for monitoring cell-substrate impedance; and

b) a sub-system comprising:

i) at least one pair of electrodes adapted for insertion into a first well on said substrate; and

(ii) circuitry adapted for applying a low-voltage, AC signal across said first pair of electrodes when said electrodes are submerged in solution medium in said first well, and for synchronously measuring the current across said electrodes,

wherein said system can be used to monitor attachment, growth or metabolic activity of cells contained in each well.

279. A method for monitoring cell attachment, growth or metabolic activity, which method comprises:

a) providing a system of Claim 277;

b) placing a solution comprising cells to be monitored into at least one well of said system ; and

c) monitoring cell-substrate impedance and solution conductivity in said well to monitor attachment, growth or metabolic activity of cells contained in each well.

280. A method for monitoring cell attachment, growth or metabolic activity, which method comprises:

a) providing a system of Claim 278;

b) placing a solution comprising cells to be monitored into at least one well of said system ; and

c) monitoring cell-substrate impedance and solution conductivity in said well to monitor attachment, growth or metabolic activity of cells contained in each well.

281. A system for detecting cells or molecules on an electrode surface, comprising:

a) the device of Claim 16;

b) at least one impedance analyzer;

c) interface electronics comprising electronic switches to control and switch said impedance analyzer to different electrode arrays of said device.

282. The system of Claim 281, further comprising software that can enable real-time measurement or monitoring of impedance between the electrodes of said device.

283. The system of Claim 282, wherein said software has at least one of the following functions:

(a) controlling electronic switching for connecting said impedance analyzer to one of multiple electrode arrays of the present devices;
(b) controlling impedance measurement analyzer for measurement of impedance between or among electrodes at one or multiple frequencies;
(c) processing the acquired impedance data to derive appropriate biologically relevant parameters (e.g., molecular reaction index, or cell number index);
(d) displaying the results on a monitor or storing results; and
(e) automatically performing above functions 1 through 4 at regular or irregular time intervals.

284. A system for monitoring cell-substrate impedance, comprising:

a) the device of Claim 90; and
b) at least one impedance analyzer;
c) interface electronics comprising electronic switches to control and switch said impedance analyzer to different electrode structure units of said device.

285. The system of Claim 284, further comprising software that can enable real-time measurement or monitoring of impedance between the electrode structures of said devices.

286. The system of Claim 285, wherein said software has at least one of the following functions:

(a) controlling electronic switching for connecting said impedance measuring circuits to one of multiple electrode structure units of the present devices;

(b) controlling impedance analyzer for measurement of impedance between or among electrode structures at one or multiple frequencies;
(c) processing the acquired impedance data to derive appropriate biologically relevant parameters (e.g., molecular reaction index, or cell number index);
(d) displaying the results on a monitor or storing results; and
(e) automatically performing above functions 1 through 4 at regular or irregular time intervals.